requested for the following reasons.

The Examiner is urged to appreciate that the present application is a U.S. national phase of PCT/GB99/01743, such that the international principles and requirements of unity of invention apply in determining patentable distinctness.

The restriction is based on the assertion by the Examiner that: (i) the common technical feature is an acid sensitive cation channel capable of reversibly mediating a rapid and sustained current, and (ii) this is disclosed by Waldman et al (1997) which is discussed in the application on page 1.

In fact, the common technical feature is the novel SPASIC ion channel (Seq ID 2) cloned by the present inventors.

This channel, in terms of its modest shared sequence identity (43% - see page 2 of application), its unique activity (see pages 2-3 bridging of the application) and its particular distribution (see page 3 of the application) represents a quite **different** , and patentably distinct, channel to Waldman's ASIC channel.

Even the existence of the SPASIC channel (as a distinct entity to the ASIC channel) was not in any way suggested by Waldman or the results therein. Since the channel was not even envisaged in the prior art, it certainly cannot be said to have been obvious or disclosed by it.

This being the case, the applicants submit that the SPASIC ion channel *per se* indisputably represents inventive subject matter. Since the claims are all based, in one way or another, on the novel and inventive SPASIC channel, they have unity. More specifically regarding R13.1 & R13.2 PCT, which are controlling in the present case for determining whether the Examiner's restriction requirement is proper, sustainable and

well-based. The claimed proteins (defined by the Examiner's Group I) and nucleic acids (defined by the Examiner's Group II) have unity of invention. The special technical feature which they share is the sequence of amino acids in the proteins which is an essential structural element of the proteins which is encoded by an exactly corresponding sequence of codons in the nucleic acids. What's more, the proteins can be generated from the nucleic acids by means of the well defined process steps (transcription and translation) which ensure that that product exactly corresponds to the starting material, i.e., a particular DNA can only encode a single protein. Thus, the two groups are technically related, and clearly fall within the scope of the examples given in Annex B in the PCT administrative instructions, or in MPEP at 1850. The subject matter of the Examiner's Group III is based on the same special technical feature, i.e., sequence of the nucleic acid encoding the protein. The subject matter of the Examiner's Group IV is based on the same special technical feature, i.e., sequence of the protein. The subject matter of the Examiner's Group V (binding molecules) also share this feature. Essentially, the part of an antibody which distinguishes it from the "prior art" is its antigen-binding site. This is an essential structural element of the antibody. The antigen-binding site of the antibodies of the Examiner's Group V will complement precisely the structure of the epitopes of the proteins of the Examiner's Group I used to raise them. This essential structural element of the Examiner's Group V antibodies is effectively incorporated therein by the subject matter of the Examiner's Group I conjugates in a single process (immunogenic presentation of the conjugate). Thus the chemical structure (primary sequence) of the protein itself is again the significant special technical feature relating the two groups. Again it is submitted that two groups fall within

the scope of the examples given in Annex B in the PCT administrative instructions, which are controlling in the present case.

Withdrawal of the restriction requirement and examination of all the claimed subject matter are requested.

In the event the Examiner refuses to withdrawal the restriction requirement, the Examiner is requested to allow rejoinder and allowance of the process claims which make and/or use the claimed product, once allowable product claims are identified. The Examiner is further requested to allow amendment of any such method claims, at an appropriate time, to expedite rejoinder and allowance of such method claims.

Reconsideration and withdrawal of the restriction requirement are requested along with an early and favorable action on the merits of all the pending claims.

Respectfully submitted,

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MARKED-UP CONPY OF AMENDED CLAIMS

7. (Amended) A nucleic acid as claimed in claim 5 which encodes a [the] SPASIC variant [of claim 3] protein which (i) has ion channel activity, and (ii) comprises an amino acid sequence having at least 80% sequence identity with the full length sequence as shown in SEQ ID NO:2 .

9. (Amended) A nucleic acid as claimed in claim 7 [or claim 8] which is an allelic variant.

16. (Amended) A method of identifying and/or cloning a [the] nucleic acid [according to any one of claims 7 to 9] which encodes a SPASIC variant protein which (i) has ion channel activity, and (ii) comprises an amino acid sequence having at least 80% sequence identity with the full length sequence as shown in SEQ ID NO:2 , or a nucleic acid which is capable of hybridizing with the complement of a nucleic acid comprising bases 292-1909 of SEQ ID NO:1 or a degeneratively equivalent sequence thereof under high stringency conditions of 0.1 x SSC, 0.5% SDS 68°C, or an allelic variant of said sequences, which method employs [the] a first nucleic acid molecule of any one of claims 11 to 15.

17. (Amended) A method as claimed in claim 16 comprising the steps of:

(a) providing a preparation of nucleic acid,

(b) providing said first [the] nucleic acid molecule [of any one of claims 11 to 15],

(c) contacting nucleic acid in said preparation with said nucleic acid molecule under conditions for hybridization,

(d) identifying said SPASIC variant if present by its hybridization with said nucleic acid molecule.

18. (Amended) A method as claimed in claim 16 comprising the steps of:

(a) providing a preparation of nucleic acid,

(b) providing a pair of nucleic acid molecule primers suitable for PCR, at least one said primers being said first [the] nucleic acid molecule [of any one of claims 12 to 15],

(c) contacting nucleic acid in said preparation with said primers under conditions for performance of PCR,

(d) performing PCR and determining the presence or absence of an amplified PCR product.

19. (Amended) A method as claimed in claim 17 [or 18] wherein the nucleic acid preparation is derived from dorsal root ganglia or spinal cord.

20. (Amended) A method of producing a derivative nucleic acid [acid] according to claim 7 [or claim 8], which method comprises the step of modifying a nucleic acid comprising Seq ID No 1.

31. (Amended) A method [as claimed in claim 30] of influencing the electrophysiological and/or pharmacological properties of a cell, said method comprising the step of causing or allowing expression of a heterologous nucleic acid of [comprising the use of any of (i)] all or part of the nucleic acid of claim 10 to reduce the activity by an anti-sense mechanism[, (ii) part of the nucleic acid of any one of claims 5 to 9 to reduce activity by co-suppression, or (iii) use of a ribozyme specific for a nucleic acid of any one of claims 5 to 9].

32. (Amended) A transgenic non-human mammal, comprising a cell of [any one of] claim[s] 24 [to 27 and/or a cell in which the electrophysiological and/or pharmacological properties has been altered in accordance with the method of any one of claims 28 to 31].

33. (Amended) A method for identifying a substance having ion-channel modulating activity, the method comprising the use of any of [(i)] the protein of any one of claims 1 or 2 [to 4, (ii) a cell of any one of claims 24 to 27, (iii) a cell in which the electrophysiological and/or pharmacological properties has been altered in accordance with the method of any one of claims 28 to 31 (iv) the 10 transgenic organism of claim 32].

34. (Amended) A method as claimed in claim 33 comprising the steps of: (i) exposing the protein [of any one of claims 1 to 4], which is associated with a membrane or cell surface, to a solution of the substance such as to allow interaction between the substance and the protein, (ii) measuring the electrophysiological response of the cell or membrane to this interaction.

35 (Amended) A method as claim in claim 33 [or claim 34] for screening for potential analgesics; neuromodulatory agents; anti-inflammatory agents; agents that regulate neurotransmitter release or neuronal excitability.

38. (Amended) Nucleic acid of [any one of] claim[s] 5 [to 10], or [the] vector ['of any one of claims 21 to 23] containing the same, for use in gene therapy, or for use in the preparation of a medicament for use in gene therapy.

39. (Amended) The nucleic acid or vector of claim [39] 38 wherein the therapy comprises the step of inhibiting a pain response and/or altering neurotransmitter release.